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Original Article

A single-arm, open-label study to assess the immunogenicity, safety, and efficacy of etanercept manufactured using the serum-free, high-capacity manufacturing process administered to patients with rheumatoid arthritis

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Abstract

Objective: To evaluate the immunogenicity, safety, and efficacy of etanercept (ETN) manufactured using the serum-free, high-capacity manufacturing (SFHCM) process in patients with rheumatoid arthritis (RA).

Methods: In this global, multicenter, open-label, single-arm study (NCT02378506), 187 adult patients with moderate to severe RA received ETN 50 mg once weekly for 24 weeks manufactured using the SFHCM process. Immunogenicity (presence of antidrug antibodies (ADAs) and neutralizing antibodies (NAbs)) was assessed at 12 and 24 weeks. Safety and efficacy were evaluated at 4, 12, and 24 weeks.

Results: Eight (4.5%) patients tested positive for ADA, and there were no NAbs detected at any time throughout the study. Ninety (48.1%) patients reported treatment-emergent adverse events (AEs), of which 27 (14.4%) reported injection-site reactions, and 43 (23.0%) reported infections. The majority of AEs were mild or moderate in severity, and the drug was well tolerated. Throughout the duration of the study (week 4 to week 24), there was a progressive increase in the American College of Rheumatology (ACR)-defined responses (ACR20: 55.9%–82.0%, ACR50: 16.1%–57.8%, and ACR70: 3.2%–26.7%) from baseline and the proportion of patients achieving low disease activity and remission, with a corresponding decrease in measures of disease activity.

Conclusion: The immunogenicity, safety, and efficacy of ETN manufactured using the SFHCM process were similar to the current approved ETN formulation. ClinicalTrials.gov registration: NCT02378506.

Keywords: Rheumatoid arthritis, etanercept, serum-free manufacturing

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Introduction

It is a common part of managing the life cycle of a biological drug, as with all medications, to undergo revisions to the manufacturing processes (1), all of which are strictly regulated (2). Etanercept (ETN) is a dimeric, human recombinant fusion protein that binds specifically to tumor necrosis factor (TNF) and lymphotoxin, inhibiting their interaction with cell surface receptors (3, 4). ETN has been manufactured using a number of processes since its approval in 1998, with each change reflecting technological developments to improve process robustness and to ensure product safety and supply. The last major ETN manufacturing change was the introduction of the serum-free process (SFP) (European Medicines Agency/H/C/262/II/83, approved on February 28, 2008) (5). The current modifications to the manufacturing process have been made to allow for an increase in the yield of drug substance from the same cell bank used in manufacturing the current ETN. There were no changes to the drug product formulations as a result of the introduction of the new manufacturing process for the drug substance.

Treatment with biological agents, including TNF inhibitors, such as ETN, has proven to be effective by reducing disease activity and improving patient quality of life in those who have not responded well to conventional disease-modifying antirheumatic drugs (DMARDs) (6-9). TNF inhibitors and other bi-

ological agents have an inherent capacity to be immunogenic. Thus, there is a potential to elicit unwanted immune responses, including the development of antidrug antibodies (ADAs), which may raise safety concerns for the patient as well as interfere with drug efficacy (10-12). Some ADAs do not affect drug activity and are designated as non-neutralizing, whereas other ADAs can become neutralizing antibodies (NAbs) negatively affecting the ability of the biological agent to bind to its target (13). Several studies have demonstrated that the presence of ADA in patients with rheumatoid arthritis (RA) treated with TNF inhibitors resulted in subtherapeutic serum drug levels and loss of efficacy, usually referred to as secondary failure (14-17). The presence of ADA was not linked to reduced clinical response in studies reporting ADA against ETN (15-17). The presence of ADAs may also contribute to the incidence of adverse events (AEs), such as injection-site and infusion reactions, thromboembolic events, and serum sickness (11, 18, 19).

Studies of the current commercially available SFP formulation of ETN reported ADAs in approximately 5% of patients with RA after 24 weeks of treatment, none of which were neutralizing (15-17). Although ETN produced by the serum-free, high-capacity manufacturing (SFHCM) process has no new structural features and is, therefore, predicted not to have an altered immunogenicity profile compared with the current SFP ETN, the present study was conducted to demonstrate that it is clinically similar to ETN manufactured by the current process so that it may be administered safely and with confidence to the patients. We report on the immunogenicity, safety, and efficacy of ETN manufactured by the SFHCM process administered at the same dose (50 mg once weekly (QW)) as the current commercially available ETN to ETN naïve patients with RA.

Methods

Study design

This was a global, multicenter, open-label, single-arm study (NCT02378506) conducted in 29 centers in nine countries (Bulgaria, Croatia, Germany, Greece, Hungary, Poland, Serbia, Slovakia, and South Africa) from April 2015 to June 2016. The study was conducted in accordance with the Declaration of Helsinki. Ethics committee approvals for this study were received from the relevant regulatory bodies in each country (see Appendix at the last page). Informed consent was obtained from all of the patients who participated in the study.

All eligible patients were screened within 4 weeks prior to the first dose. Patients were administered ETN 50 mg QW subcutaneously for 24 weeks. Immunogenicity (ADAs and NAbs) was measured at baseline and subsequent visits at 12 and 24 weeks. The efficacy, safety, and patient-reported outcomes were measured at baseline and subsequent visits at 4, 12, and 24 weeks. A safety follow-up was conducted via telephone 28-32 days after 24 weeks or early withdrawal visit.

Patients

Adult patients with active moderate to severe RA (disease activity score based on 28 joint count (DAS28) ≥3.2, tender joint count (TJC) ≥4, and swollen joint count (SJC) ≥4) at screening and baseline visits, who had not been treated previously with ETN, and with normal laboratory results were enrolled in the study. Patients who were previously treated with ETN, received methotrexate >25 mg/week or had a change in dose or route of administration of methotrexate within 6 weeks of the first study dose, had a dose change in permitted conventional synthetic DMARDs within 4 weeks of the first study dose, received cyclophosphamide, cyclosporine, or azathioprine within 6 months of the first study dose, received TNF inhibitor or any other biological treatment for RA within 12 weeks of the first study dose, received any biological B cell-depleting agent (e.g., rituximab) within 2 years of the first study dose, received corticosteroids within 4 weeks of the first study dose, received nonsteroidal anti-inflammatory drugs more than the maximum recommended dose, or received live (attenuated) vaccines within 4 weeks of the first study dose were excluded from the study. Patients with serious infections within 4 weeks, with active infections at the time of screening or baseline visits, with active or latent tuberculosis, or with any medical condition that could interfere with the assessments were also excluded.

Assessments

ETN concentration was measured from serum samples collected prior to the first dose and after 12 and 24 weeks of treatment or upon early withdrawal, using a validated enzyme-linked immunosorbent assay (ELISA). Serum samples used to test for ADAs to ETN were collected simultaneously in order to minimize the potential drug effect and were assayed using the same validated ELISA used throughout the development of ETN. During the most recent cross-validation, the assay precision for the negative control, expressed as the between-day percent coefficient of variation, was 20.2%.

Samples were deemed positive if the optical density was two times than what was observed in the pre-treatment samples. There was no distinction between the positive samples of different titers. All samples testing positive for ADA were subsequently evaluated for the presence of Nabs using a validated ELISA. During the most recent cross-validation, the assay precision for the negative control was ≤13.3%. All assays were conducted by Celerion (formerly MDS Pharma Services, Lincoln, NE, USA).

The incidence and severity of all AEs and serious AEs (SAEs) were recorded, and the abnormal test findings, laboratory evaluations, and vital signs were monitored. The efficacy of treatment was determined as 20%, 50%, and 70% improvements from baseline in the American College of Rheumatology (ACR) criteria for RA (ACR20, ACR50, and ACR70, respectively), DAS28 by erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), number of TJC and SJC, Physician Global Assessment (PGA), Patient Global Assessment (PtGA), Health Assessment Questionnaire-Disability Index (HAQ-DI), patient general health, and patient pain assessed using a Visual Analog Scale (VAS).

Statistical analysis

Approximately 180 patients were enrolled to provide 162 evaluable patients. Assuming that the true incidence of ETN ADA formation was ≤5%, the probability of obtaining an estimate of >10% was not >0.33%. If the true incidence of ETN ADA formation was ≥10%, the probability of obtaining an estimate of ≤5% was not >1.54%. This number of patients would also provide 80% probability of observing one or more safety events with an incidence of ≥1%. Events and response proportions are presented as percentages (%) with 95% confidence intervals. For composite endpoints, including the DAS28-CRP and ACR responses, missing values of component parameters were carried forward from the previous visit. There was no formal statistical testing planned. A life-table estimate of the cumulative incidence of antibody formation through 12 and 24 weeks was performed to adjust the estimate for incomplete data. The life-table analysis accounted for when subjects completed the ADA evaluations and whether subjects discontinued the study early, prior to the protocol-specified 24 weeks of the study duration of treatment.

Results

Patients

A total of 188 patients were enrolled in the study. Of the patients, 163 (86.7%) completed the study (Figure 1). One patient withdrew

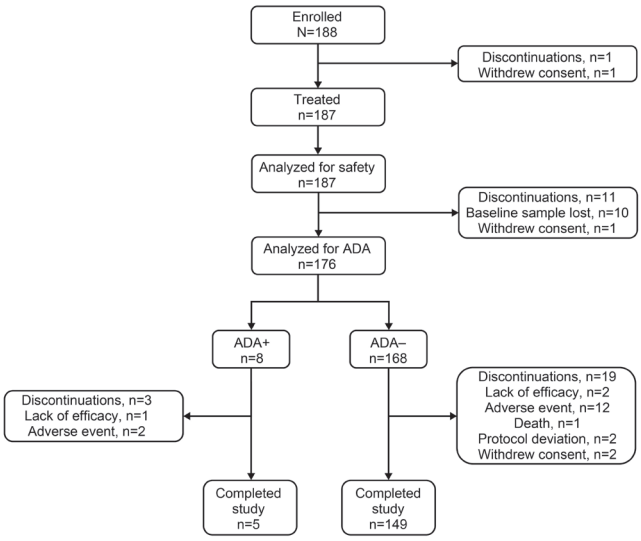

Figure 1. Patient disposition
ADA: antidrug antibody

Table 1. Baseline patient characteristics by ADA status*

	Total (n=187)**	ADA+(n=8)	ADA - (n=168)
Age (years)	54.2 (12.9)	58.8 (15.0)	54.2 (12.5)
Female, n (%)	159 (85.0)	6 (75.0)	145 (86.3)
Race, n (%)			
White	179 (95.7)	8 (100.0)	160 (95.2)
Black	0 (0.0)	0 (0.0)	0 (0.0)
Asian	4 (2.1)	0 (0.0)	4 (2.4)
Other	4 (2.1)	0 (0.0)	4 (2.4)
Baseline BMI (kg/m2)	27.3 (5.2)	27.2 (6.2)	27.5 (5.3)
Disease duration (years)	8.0 (7.2)	10.3 (13.0)	7.8 (7.0)
Prior medications, n (%)			
Non-biological DMARDs	96 (51.3)	2 (25.0)	87 (51.8)
Biological DMARDs	29 (15.5)	3 (37.5)	26 (15.5)
Corticosteroids	97 (51.9)	0 (0.0)	89 (53.0)
Methotrexate	169 (90.4)	8 (100.0)	152 (90.5)
RF positive, n (%)	116 (62.0)	3 (37.5)	108 (64.3)
Anti-CCP positive, n (%)	126 (67.4)	3 (37.5)	117 (69.6)
ESR (mm/h)	36.1 (22.1)	36.0 (26.4)	34.9 (21.6)
CRP (mg/L)	11.2 (16.0)	17.2 (22.1)	10.6 (14.9)
TJC	14.2 (6.0)	16.0 (6.3)	13.9 (6.1)
SJC	10.9 (5.2)	13.2 (7.1)	10.6 (5.1)
DAS28-ESR	6.2 (0.9)	6.5 (0.9)	6.1 (0.9)
DAS28-CRP	5.4 (0.9)	5.9 (1.0)	5.3 (0.9)

*Data were presented as mean (SD), unless otherwise stated

**The total numbers do not add up to the other two columns because the ADA data for 11 patients were not available

ADA: antidrug antibody, BMI: body mass index, CCP: cyclic citrullinated peptide, CRP: C-reactive protein, DAS28: disease activity score based on 28 joint count, DMARD: disease-modifying antirheumatic drug, ESR: erythrocyte sedimentation rate, RF: rheumatoid factor, SD: standard deviation, SJC: swollen joint count, TJC: tender joint count

consent prior to any drug administration. An additional 22 patients discontinued during the study, with 3 (1.6%) for lack of efficacy, 14 (7.4%) due to AEs, 2 (1.1%) for protocol deviation, 1 (0.5%) died, 4 (2.1%) for withdrawal of consent, and 1 (0.5%) for other reasons. The baseline patient characteristics (Table 1) were similar to published patient characteristics for studies demonstrating ETN efficacy and safety in patients with RA (6-9). Overall, 153 (81.8%) patients received concomitant methotrexate during the study.

Immunogenicity

The median duration of treatment was 23 (21.6±5.0) weeks. Data on the ADA status during the course of the study were missing for 11 patients, with 10 due to mishandling of the baseline sample and 1 withdrew consent at 4 weeks. The baseline patient characteristics for patients testing positive for ADA are comparable to those testing negative (Table 1). Of the 176 patients for whom immunogenicity data were available (at least one ADA assessment), 8 (4.5%) tested positive for ADA at any time throughout the study (Table 2), all of whom were receiving concomitant methotrexate. Of these 8 patients, 3 (1.7%) tested positive at 12 weeks (individual ADA titers of 200, 400, and 400 arbitrary units (AU)/mL), and 5 (2.8%) more tested positive at 24 weeks or early termination (individual ADA titers of 100, 200, 400, 400, and >400 ADA AU/mL). High and low ADA titers were not distinguished, as all positive samples were subsequently tested, and all were found to be negative for NAbs. Since early termination can occur at any time during the study, some patients tested positive for ADA prior to 12 weeks. The cumulative incidence rates were 3.64% up to 12 weeks and 6.16% up to 24 weeks using a life-table analysis.

The mean±standard deviation (SD) concentrations of ETN at 12 weeks were 1.5±0.2 µg/mL among patients testing positive for ADA (n=3) and 2.3±1.3 µg/mL among those testing negative for ADA (n=154; p=0.29). At 24 weeks or early termination, the mean±SD concentrations were 1.0±0.5 µg/mL (n=5) and 2.3±1.7 µg/mL (n=158; p=0.02), respectively.

Safety

Table 3 summarizes all-cause treatment-emergent AEs (TEAEs). A total of 90 (48.1%) patients reported 196 TEAEs, 27 (14.4%) patients reported 48 injection-site reactions, 43 (23.0%) patients reported 50 investigator-identified infections, and 56 (29.9%) patients reported 98 other AEs. Nine (4.8%) patients reported 11 SAEs, with lymphadenopathy, acute cardiac failure, metatarsalgia, osteoarthritis, major

Table 2. Summary of the incidence of patients developing ADA against ETN by methotrexate treatment status*

	All patients (n=176)	No methotrexate (n=16)	Methotrexate (n=160)
Total	4.5 (2.2-8.4)	0.0 (0.0-14.3)	5.0 (2.4-9.2)
At 12 weeks	1.9 (0.5-5.0)	0.0 (0.0-16.2)	2.1 (0.6-5.5)
At 24 weeks or early termination	2.9 (1.1-6.1)	0.0 (0.0-14.3)	3.1 (1.2-6.8)
At any time	4.5 (2.2-8.4)	0.0 (0.0-14.3)	5.0 (2.4-9.2)

*Data were presented as percentage (%, 95% CI)

ADA: antidrug antibody, CI: confidence interval, ETN: etanercept

Table 3. Total

	Total	Injection-site reactions	Infections	All other
Total no. of AEs	196	48	50	98
Patients with AEs	90 (48.1)	27 (14.4)	43 (23.0)	56 (29.9)
Patients with SAEs	9 (4.8)	0 (0.0)	3 (1.6)	8 (4.3)
Patients with severe AEs	6 (3.2)	0 (0.0)	0 (0.0)	6 (3.2)
Patients discontinuing due to AEs	14 (7.5)	3 (1.6)	2 (1.1)	9 (4.8)
Patients with temporary discontinuation due to AEs	21 (11.2)	0 (0.0)	18 (9.6)	5 (2.7)

*Data were presented as n (%)

AE: adverse event, SAE: serious adverse event, TEAE: treatment-emergent adverse event

depression, ureteric calculus, urticaria, deep vein thrombosis, diverticulitis, pneumonia, and wound infection for each. Six (3.2%) patients reported severe AEs, with urticaria, lymphadenopathy, acute cardiac failure, retinal detachment, back pain, and allergic dermatitis for each. Fourteen (7.5%) patients experienced an AE leading to discontinuation, with three due to injection-site reactions, two due to infections, and one each due to urticaria, lymphadenopathy, acute cardiac failure, macular rash, depression, allergic dermatitis, pruritic rash, thrombocytopenia, and one worsening of RA, and one death was due to acute heart failure. Fifty-two (27.8%) patients experienced an AE considered by the investigator to be drug-related. There were no TEAEs of opportunistic infections, malignancies, demyelinating disorders, or prespecified events of clinical importance reported. The majority of AEs were mild or moderate in severity.

Efficacy

Overall, the proportions of patients achieving ACR20, ACR50, and ACR70 increased progressively over time (Figure 2a), accompanied by a decrease in DAS28-ESR and DAS28-CRP scores (Figure 2b) and an increase in the proportion

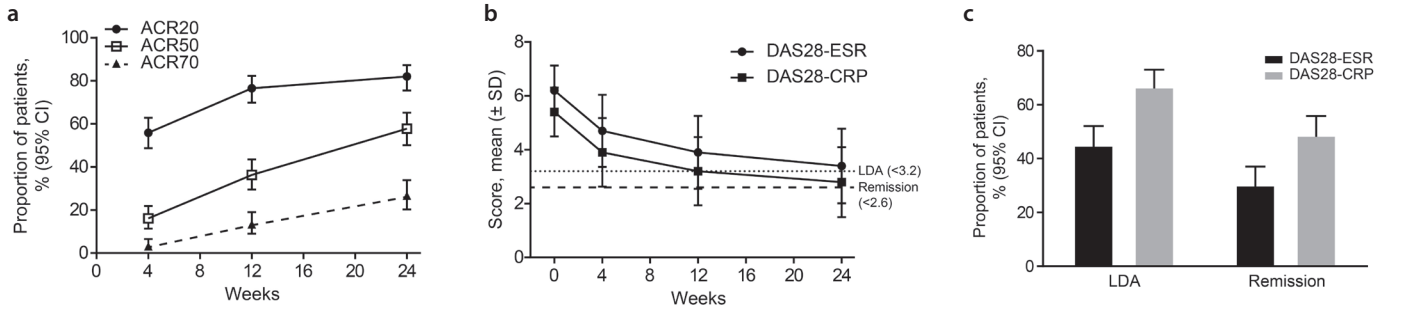

Figure 2. a-c. Clinical responses

Proportions of patients achieving ACR20, ACR50, and ACR70 (b); DAS28-ESR and DAS28-CRP scores (b); proportions of patients achieving LDA and remission according to the DAS28-ESR and DAS28-CRP criteria at 24 weeks (c). For composite measures, missing component values were imputed using the last observation carried forward

ACR20; ACR50; ACR70: American College of Rheumatology criteria for RA, CRP: C-reactive protein, DAS28: disease activity score based on 28 joint count, ESR: erythrocyte sedimentation rate, LDA: low disease activity, SD: standard deviation

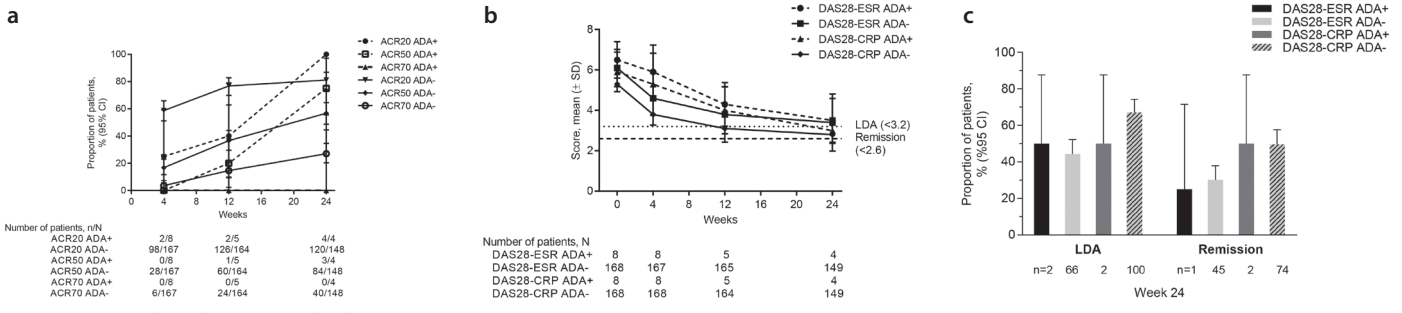

Figure 3. a-c. Clinical responses by the ADA status

Proportions of ADA+ and ADA- patients achieving ACR20, ACR50, and ACR70 (a); DAS28-ESR and DAS28-CRP scores in ADA+ and ADA- patients (b); proportions of ADA+ and ADA- patients achieving LDA and remission according to the DAS28-ESR and DAS28-CRP criteria at 24 weeks (c). For composite measures, missing component values were imputed using the last observation carried forward

ACR20; ACR50; ACR70: American College of Rheumatology criteria for RA, ADA: antidrug antibody, CRP: C-reactive protein, DAS28: disease activity score based on 28 joint count, ESR: erythrocyte sedimentation rate, LDA: low disease activity, SD: standard deviation

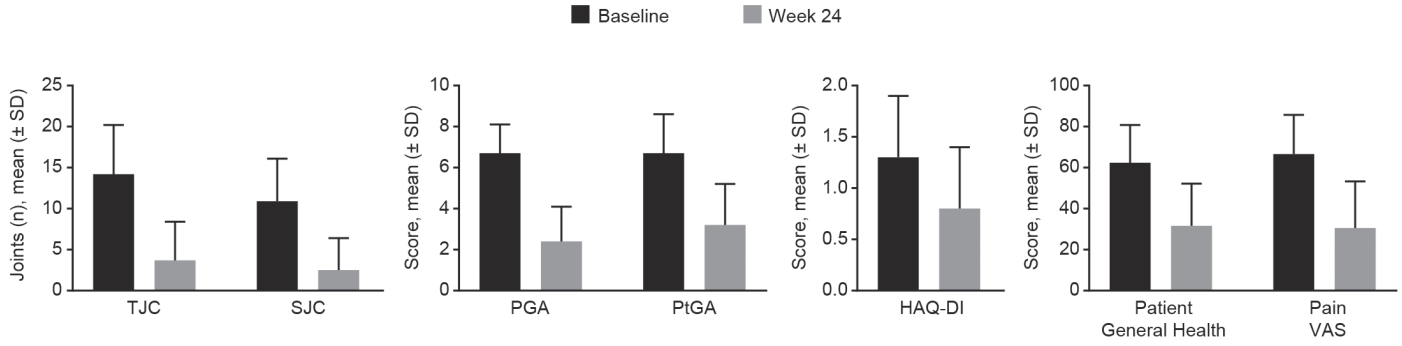

Figure 4. Summary of efficacy assessments at 24 weeks
HAQ-DI: Health Assessment Questionnaire-Disability Index, PGA: Physician Global Assessment, PtGA: Patient Global Assessment, SD: standard deviation, SJC: swollen joint count, TJC: tender joint count, VAS: Visual Analog Scale

of patients achieving low disease activity (LDA; <3.2) and remission (<2.6) according to both DAS28-ESR and DAS28-CRP criteria (data not shown). At 24 weeks, 44.4% (72/162) and 66.0% (107/162) of patients achieved LDA, as measured via DAS28-ESR and DAS28-CRP, respectively, and 29.6% (48/162) and 48.1% (78/162) achieved disease remission (Figure 2c).

When analyzed by the ADA status, a progressive increase in ACR20 and ACR50 responses was observed over time for patients testing positive and negative for ADA (Figure 3a). However, there was no patient testing positive for ADA who achieved an ACR70 response at any time point (Figure 3a). DAS28-ESR and DAS28-CRP scores decreased progressively over time in both patients testing positive and negative for ADA (Figure 3b). At 24 weeks, 50.0% (2/4) of patients testing positive for ADA achieved LDA, as measured via DAS28-ESR and DAS28-CRP, compared with 44.3% (66/149) and 67.1% (100/149) of patients testing negative for ADA, respectively (Figure 3c). Furthermore, 25.0% (1/4) and 50.0% (2/4) of patients testing positive for ADA achieved disease remission, as measured via DAS28-ESR and DAS28-CRP, respectively, compared with 30.2% (45/149) and 49.7% (74/149) of patients testing negative for ADA (Figure 3c).

Over the course of the study, there were consistent decreases in TJC and SJC, as well as decreases in scores for PGA, PtGA, HAQ-DI, patient's assessment of general health, and pain VAS (Figure 4).

Discussion

The present study assessed the immunogenicity, safety, and efficacy of ETN manufactured using the SFHCM process in 187 subjects with moderate to severe RA during 24 weeks of administration. We compared the immunogenicity, safety, and efficacy of ETN manufactured by the SFHCM process with historical results. The current commercially available ETN induces a significantly lower immunogenic response, with the development of fewer ADAs, than anti-TNF monoclonal antibodies (20). Furthermore, treatment with the current commercial formulation of ETN has not been associated with the development of detectable NAbs (7, 16).

The incidence of 8 (4.5%) patients developing ADA is consistent with findings for ETN manufactured using the current manufacturing process, which report up to 5% of patients developing ADA (7, 21). It is not surprising that all eight patients were receiving concomitant methotrexate, since >81% of patients were in this group. Importantly, from a clinical efficacy point of view, none of the patients treated in the present study developed NAbs. In addition, importantly, the ETN used in the present study was well tolerated, with most of the AEs being mild or moderate in severity. These data are also consistent with published studies (7, 11, 14-17). These results confirmed that ETN manufactured by the SFHCM process retained low immunogenicity potential and a favorable risk-to-benefit ratio when compared with the current commercially available ETN.

The efficacy of ETN manufactured using the SFHCM process, shown as improvements in ACR response, DAS28 score, and other efficacy parameters, was similar to that observed in controlled clinical trials with similar enrollment criteria (6-9). However, the presence of ADAs appeared to reduce the therapeutic response to ETN as measured by ACR, as no patients who developed ADAs achieved an ACR70 response at any time point, unlike the patients who did not develop ADAs. There were no significant differences in decreased disease activity, as measured using DAS28, between patients who developed ADAs and those who did not. However, it is important to note that no formal efficacy comparisons were planned or performed between patients with and without ADAs due to the small number of patients who were expected to develop ADAs after treatment with ETN that was manufactured using the SFHCM process. Consistent with published studies, ETN manufactured in this SFHCM process was well tolerated (6-9). Our study was conducted in a population of patients with characteristics that have been well established for the evaluation of new biological agents for the treatment of RA, including a relatively low proportion (15.5%) of patients exposed to prior biological DMARDs and a high proportion of patients receiving concomitant glucocorticoids (51.9%) and methotrexate (90.4%). In addition, the single-arm, open-label study design must be taken into consideration when interpreting the efficacy results. Finally, although the ELISA methodology used to measure ETN levels and ADA/NAb titers is widely used and recognized as reliable, it does have some limitations, including non-specific binding and failure to detect low-affinity antibodies (22). However, we believe that the comparison of ETN concentrations and ADA frequency results from the present study with those from previous ETN studies is justified because the same ELISA methodology has been used throughout the development of ETN.

When compared with historical data on the current commercially available ETN, this single-arm, open-label study with ETN manufactured using the SFHCM process has succeeded in meeting all the objectives pertaining to immunogenicity, safety, and efficacy. Changes in the manufacturing processes are needed to take advantage of new technologies and to maintain adequate supplies of medications for patients. Strictly regulated revision of changes in the manufacturing process of ETN, as with other therapeutic agents, is a common part of the ongoing aim to keep an established medicine safe and efficacious while improving manufacturing. This is important for clinical consistency so that both physicians and patients can be confident about the reproducibility and reliability of the safety and efficacy results when

prescribing or receiving ETN manufactured via a new process.

Ethics Committee Approval: Ethics committee approvals for this study were received from the relevant regulatory bodies in each country (see Appendix at the last page).

Informed Consent: Written informed consent was obtained from subjects who participated in this study.

Peer-review: Externally peer-reviewed

Author Contributions: Concept - B.V., P. Polák; Design - P. Polák, B.V., R.P., J.K.B.; Supervision - T.W., S.M.G., J.C.B., J.K.B., B.V.; Data Collection and/or Processing - P. Polák, P. Perić, I.L., S.M.G., T.W., J.C.B.; Analysis - R.P.; Interpretation - P. Polák, P. Perić, I.L., S.M.G., T.W., J.C.B., J.K.B., R.P., B.V.; Writing Manuscript - P. Polák, R.P., B.V.; Critical Review - P. Polák, P. Perić, I.L., S.M.G., T.W., J.C.B., J.K.B., R.P., B.V.

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Conflict of Interest: P. Polák is the primary external reviewer and a consultant for Pfizer on this study and principal investigator. P. Peric is a principal investigator and a consultant for Pfizer on this study. I.L. is an advisor in rheumatology for Bristol-Myers Squibb, Novartis, Pfizer, and Roche, and a principal investigator on clinical studies sponsored by Amgen, AstraZeneca, Baxalta, Bristol-Myers Squibb, Celgene, Coherus, Eli Lilly, Janssen, and Pfizer. J.C.B. is an employee of Becker Clinical Research Consulting LLC, who was a paid consultant to Pfizer in connection with the development of this manuscript and owns stock in Pfizer. S.M.G., T.W., R.P., J.K.B., B.V. are employees of Pfizer and own stock in Pfizer.

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You can reach the appendix table of this article at https://doi.org/10.5152/eurjrheum.2018.18078

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Appendix.

Table A1. List of IEC/IRB Approvals by Country and Study Site

Country	Study Site Number	IEC or IRB	Approval Date
Bulgaria	1052	Republic of Bulgaria Ministry of Health Ethics Committee for Multicenter Trials Sofia, BULGARIA	25-MAR-15
	1061	Republic of Bulgaria Ministry of Health Ethics Committee for Multicenter Trials Sofia, BULGARIA	10-JUN-15
	1071	Republic of Bulgaria Ministry of Health Ethics Committee for Multicenter Trials Sofia, BULGARIA	10-JUN-15
	1072	Republic of Bulgaria Ministry of Health Ethics Committee for Multicenter Trials Sofia, BULGARIA	25-MAR-15
Croatia	1062	Central Ethics Committee Agency For Medicinal Products And Medical Devices Zagreb, CROATIA	24-FEB-15
	1094	Central Ethics Committee Agency For Medicinal Products And Medical Devices Zagreb, CROATIA	24-FEB-15
	1096	Central Ethics Committee Agency For Medicinal Products And Medical Devices Zagreb, CROATIA	16-APR-15
Germany	1053	Ethikkommission der Medizinischen Hochschule Hannover Hannover, GERMANY	7-APR-15
	1054	Ethikkommission der Medizinischen Hochschule Hannover Hannover, GERMANY	7-APR-15
	1073	Ethikkommission der Medizinischen Hochschule Hannover Hannover, GERMANY	7-APR-15
	1091	Ethikkommission der Medizinischen Hochschule Hannover Hannover, GERMANY	7-APR-15
	1092	Ethikkommission der Medizinischen Hochschule Hannover Hannover, GERMANY	7-APR-15
Greece	1004	National Ethics Committee Athens, GREECE	31-JUL-15
	1007	National Ethics Committee Athens, GREECE	5-MAY-15
	1081	National Ethics Committee Athens, GREECE	5-MAY-15
Hungary	1005	Medical Research Council Ethics Committee for Clinical Pharmacology Budapest, HUNGARY	22-JAN-15
	1059	Medical Research Council Ethics Committee for Clinical Pharmacology Budapest, HUNGARY	22-JAN-15
	1064	Medical Research Council Ethics Committee for Clinical Pharmacology Budapest, HUNGARY	22-JAN-15

Appendix.

Table A1. List of IEC/IRB Approvals by Country and Study Site (Continued)

Country	Study Site Number	IEC or IRB	Approval Date
Poland	1065	Komisja Bioetyczna przy Okregowej Radzie Lekarskiej Wielkopolskiej Izby Lekarskiej Poznan, POLAND	17-DEC-14
	1066	Komisja Bioetyczna przy Okregowej Radzie Lekarskiej Wielkopolskiej Izby Lekarskiej Poznan, POLAND	25-MAR-15
	1074	Komisja Bioetyczna przy Okregowej Radzie Lekarskiej Wielkopolskiej Izby Lekarskiej Poznan, POLAND	2-JUN-15
	1077	Komisja Bioetyczna przy Okregowej Radzie Lekarskiej Wielkopolskiej Izby Lekarskiej Poznan, POLAND	25-MAR-15
Serbia	1067	Ethics Committee of the Institute of Rheumatology Belgrade, SERBIA	8-DEC-14
	1078	Ethics Committee of the Institute of Rheumatology Belgrade, SERBIA	8-DEC-14
Slovakia	1015	Eticka komisia Urad Presovskeho samospravneho kraja Presov, SLOVAKIA	12-JAN-15
		Eticka komisia Urad Zilinskeho samospravneho kraja Zilina, SLOVAKIA	
	1026	Eticka komisia Urad Zilinskeho samospravneho kraja Zilina, SLOVAKIA	25-NOV-14
	1028	Eticka komisia Urad Zilinskeho samospravneho kraja Zilina, SLOVAKIA	25-NOV-14
		Eticka komisia Bratislavsky samospravny kraj Bratislava, SLOVAKIA	
	1029	Eticka komisia Trnavsky samospravny kraj Trnava, SLOVAKIA	11-DEC-14
		Eticka komisia Urad Zilinskeho samospravneho kraja Zilina, SLOVAKIA	
	1080	Nezavisla eticka komisia Banskoby strickeho samospravneho kraja Banska Bystrica, SLOVAKIA	12-JAN-15
		Eticka komisia Urad Zilinskeho samospravneho kraja Zilina, SLOVAKIA	
	1088	Eticka komisia Urad Zilinskeho samospravneho kraja Zilina, SLOVAKIA	11-DEC-14

Appendix.

Table A1. List of IEC/IRB Approvals by Country and Study Site (Continued)

Country	Study Site Number	IEC or IRB	Approval Date
		Eticka komisia Trnavsky samospravny kraj Trnava, SLOVAKIA	
South Africa	1050	Pharma Ethics Independent Research Ethics committee Pretoria, SOUTH AFRICA	4-FEB-15
	1068	University of the Witwatersrand, Johannesburg Human Research Ethics Committee: (Medical) Johannesburg, SOUTH AFRICA	13-FEB-15
	1069	Pharma Ethics Independent Research Ethics committee Pretoria, SOUTH AFRICA	4-FEB-15

IEC: Independent Ethics Committee; IRB: Institutional Review Board